REMARKS

Claims 41-67, 69-75, 77-87 and 90-93 were pending in the subject application. Claims 41-48, 51-53, 56-67, 69-71, 73-87 and 90-91 were withdrawn from consideration by the Examiner as directed to non-elected subject matter. By this Amendment, applicant has canceled Claims 41-48, 51-53, 56-67, 69-71, 73-87 and 90-91 without prejudice or disclaimer. Accordingly, upon entry of this amendment, Claims 49-50, 54-55, 72 and 92-92 will be pending. The amendments to the claims do not raise an issue of new matter. Accordingly, entry of the amendments is respectfully requested.

Status of Claims 92 and 93

Claims 92 and 93 were added in applicant's Amendment in Response to May 3, 2007 Office Action, which is dated August 1, 2007. Claims 92 and 93 apparently have not been considered on their merits by the Examiner in the current Office Action. Examination of these claims is respectfully requested.

Rejections under 35 U.S.C. §103(a)

1. Claims 49 and 50 are rejected as being unpatentable over over Müller (Expert Opinion on Pharmacotherapy 3: 381-8, 2002) in view of Permax® prescribing information (2003).

Applicant respectfully traverses this rejection.

Müller - avoidance of drug interactions. Müller is an expert opinion on the complications of pharmacotherapy of combination drug therapy due to possible drug interactions (see abstract on page 381). Müller is extremely cautious on combining different drugs. In the Expert opinion (point 5 on page 385-6), it is stated that "The choice of these supplementary agents [which are not exemplified] must be considered very carefully and the titration of extra drugs must be performed very slowly and cautiously...

Sometimes reduction of dopaminergic drugs and rehydration is more beneficial than the addition of further compounds, since the increasing amount of medication often results in compliance problems.... Moreover, treatment proposals would be questionable, since tolerability of this additional medication for non-motor symptoms differs interindividually. Treating physicians often need more long-term experience for the combined use of these supplementary drugs with dopaminergic agents to achieve an improvement in quality of life and to prevent the onset of drug side effects."

It is concluded on page 386, 2nd column that "Specialist knowledge of internal medicine, psychiatry and pharmacology is advantageous in order to avoid drug interactions with antiparkinsonian medication and to guarantee adequate treatment." [Emphasis added.]

Thus, applicant maintains that Müller ***teaches against*** the use of extra medication apart from the true anti- Parkinson Disease (PD) drugs in treating PD patients.

Müller - advocating rehydration and reduction of dopaminergic drugs. Instead of drug combinations, Müller advocates reduction of dopaminergic drugs on the one hand, i.e. the true anti-PD drugs, and rehydration on the other hand. In the Expert opinion (point 5 on page 386), it is stated that "Sometimes reduction of dopaminergic drugs and rehydration is more beneficial than the addition of further compounds, since the increasing amount of medication often results in compliance problems."

On page 386, Müller continues with stating that "International standardized treatment recommendations are not available, nor are they under discussion. Moreover, treatment proposals would be questionable, since the tolerability of this additional medication for non-motor symptoms differs interindividually."

Müller ***teaches alternatives*** for combination therapies.

Müller - teaching against using pipamperone. In point 4.2 in column 1 on page 385 Müller states that "Since classical neuroleptics such as the butyrophenones [e.g. pipamperone] or phenothiazines ***increase extra-pyramidal symptoms***, atypical neuroleptics are primarily used for the psychotic symptoms in PD." [Emphasis added.]

Hence, in case a neuroleptic is to be used (which is taught against anyway), then a classical neuroleptic such as pipamperone is to be avoided, but an atypical neuroleptic is to be administered.

Thus, Müller ***teaches against*** the use of butyrophenones (including pipamperone).

Müller - confusing and incorrect with regard to pipamperone. In column 2 on page 385, it is stated that "Further treatment options are sedative antipsychotic drugs with a ***low DA receptor blocking potential***, like melperone or ***pipamperone***." [Emphasis added.]

Apart from contradicting the previous statement (see above), the latter statement is also incorrect in that pipamperone has a high affinity of the D4 receptor (see e.g. Table in application).

Müller - conclusions by the person skilled in the art. The disclosure of Müller must be considered in its complete context as detailed above, including the disclosure on pipamperone.

In view of Müller, the person skilled in the art would

(a) be discouraged from using combination medication in treating PD patients;

(b) be taught away from prescribing butyrophenones in general;

(c) be wholly confused with regard to using pipamperone; and

(d) be taught alternative therapies.

Permax® - *indications and usage*. This document states on page 1, column 1, that "Permax is indicated as an adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease."

There is no other -positive- further indication of using Permax considered by the manufacturer, such as combining Permax with other drugs (see also below).

Permax® - *warnings against drug interactions*. Under the heading "Drug interactions" on page 1, column 2, the document states that "Dopamine antagonists, such as the neuroleptics (pheonthiazines, butyrophenones [e.g. pipamperone], thioxanthines) or metoclopramide, ordinarily should ***not be administered concurrently*** with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax." [Emphasis added.]

Thus, Permax® teaches against the use of pipamperone with Permax.

Permax® - *further considerations by the person skilled in the art.*

The instructions ***warn*** on several occasions that Permax® causes symptoms of falling asleep, somnolence, drowsiness and sedation. These very same symptoms may also be experienced by using pipamperone. In view of the expected additive effects, applicant maintains that the person skilled in the art would not be tempted to use pipamperone.

Permax® - *conclusions by the person skilled in the art*. The disclosure of Permax® must be considered in its complete context as detailed above, including the disclosure on pipamperone. In view of Permax®, the person skilled in the art would

(a) only be taught using the combination Permax with levidopa/carbidopa in treating PD patients;

(b) be taught away from prescribing butyrophenones in general, which include pipamperone; and

(c) be warned against the similar negative side effects of pipamperone and Permax.

Combination and achieving the invention. In view of the teachings of both documents, applicant maintains that the person skilled in the art would never contemplate using a combination including pipamperone in treating PD. Both documents discourage using pipamperone.

After diagnosing Parkinson Disease, the MD will prescribe a drug, which is recommended for treating this diagnosed disorder. In the present case, pipamperone is ***not*** recommended for treating PD (see for instance the instructions of the manufacturer). Hence, a correct diagnosis of PD would avert the use of pipamperone.

Applicant respectfully maintains that the teaching of the prior art would never result in the present invention without applying unallowable hindsight, *i.e.* picking and choosing various elements from the prior art, using these elements out of their context, and making arbitrary combinations to construct an invention in hindsight.

Doses - increasing the dose of pipamperone. From the art and standard textbooks it can be learned that pipamperone is used as a sedative neurolepticum at a dose of 40 mg/day and higher (see for instance the instructions of the manufacturer).

Obviously, the treatment regimen will start with a dose as extensively tested and recommended by the manufacturer. Thus, the instructions of the manufacturer will provide a further guiding principle for the dose used (cf. instructions of the manufacturer). Only after several weeks of observation, the MD can evaluate whether the

prescribed dose is effective or not. In case a drug appears not to be effective, the dose will either be ***increased*** or a ***different drug*** will be prescribed.

Indeed, the instruction manual from the manufacturer advises to increase the starting dose to the maximum tolerable dose. This teaching is ***unidirectional***, *i.e.* to increase the dose of pipamperone.

Doses - effect of two compounds. In the present invention, the enhanced clinical effect is dependent upon two compounds, which act synergistically. However, at other doses, these compounds have no mutual effect, or even have opposing effects. Indisputably, this adds to the complexity of determining the effect of any dose.

Thus, determining at which dose pipamperone augments the efficacy of a second compound is certainly not routine, but either goes against the teaching in the art (e.g. pipamperone) or amounts to undue burden.

Silver (see also below) mentions on page S21, column 2 that ""start low, go slow" should be the bywords for initiating treatment. By starting with a low dose and gradually titrating ***upward*** ..." [Emphesis added.] Silver also mentions (page S21, column 2) the inherent complications of the effects of a combination therapy to "be sure to change only one drug at a time in multidrug regimen", which illustrates the inherent complications of assessing multidrug therapies.

2. Claims 54 and 55 are rejected as being unpatentable over Müller in view of Silver et al. (Neurology Vol. 50, Suppl. 6, pp S18-22, 1998).

Applicant respectfully traverses this rejection.

Applicant's discussion of Müller (above) is incorporated into the present discussion.

The Examiner asserts that Silver et al. teach that carbidopa-levodopa is used to treat PD.

Silver - advocates dopamine agonists. Silver has been discussed in applicant's previous response. In particular, applicant argued that Silver advocates treatment with dopamine ***agonists*** (in general) throughout the article. It is not specified which dopamine receptor should be activated. Hence, applicant maintains that the person skilled in the art would ***not*** use a dopamine receptor D4 ***antagonist.*** Pipamperone is a dopamine receptor D4 ***antagonist.***

Even when Silver teaches that carbidopa-levodopa is used, it is in combination with a dopamine ***agonist***. Thus, Silver provides no incentive for using a dopamine receptor D4 ***antagonist***, such as pipamperone. To the contrary, this would go against the teaching of the document.

Thus, applicant maintains that both Müller and Silver teach against the use of pipamperone. Moreover, in view of common general knowledge, the person skilled in the art is taught away from the low dose of pipamperone (see above).

3. Claim 72 is rejected as being unpatentable over Müller in view of Nystrom et al. (US 5,635,213).

Applicant respectfully traverses this rejection.

Applicant's discussion of Müller (above) is incorporated into the present discussion.

The Examiner asserts that Nystrom teaches L-dopa and benserazide as the active agents for treating PD.

Nystrom relates to a pharmaceutical composition for intraduodenal administration of L-dopa, possibly combined with carbidopa or benserazide. Nystrom is completely silent on using a further compound apart from carbidopa or benserazide, let alone a non-PD agent, and even less pipamperone.

Conclusion. Applicant respectfully maintains that Müller teaches against the use of pipamperone. Nystrom is wholly silent on using a further compound apart from carbidopa or benserazide, let alone a non-PD agent, and even less pipamperone. None of the cite documents teaches a particular dose of pipamperone.

Applicant believes that only with hindsight would the person skilled in the art be tempted to combine Müller with Nystrom. However, even if it is assumed that the person skilled in the art would combine Müller with Nystrom (which is denied), then the person would still not come to the present invention, since (i) Müller teaches against the use of pipamperone, (ii) Nystrom does not hint at using a further compound; and (iii) in view of common practice, the person skilled in the art is taught away from the low dose of pipamperone.

Reconsideration and withdrawal of these rejections are respectfully requested.

Provisional Obviousness-Type Double Patenting Rejection

Claims 50 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 and 4 of co-pending, later-filed US Patent Application No. 10/984,683, Buntinx (US 2005/0203130) .

Applicant respectfully traverses this rejection. Claim 4 of Application No. 10/984,683 has been canceled, and Claim 1 has been amended to recite:

> A method for treating a mood disorder comprising administering to a patient pipamperon in a dose ranging between 5 and 15 mg of the active ingredient, and administering said pipamperon simultaneously with, separate from or sequential to a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said SNRI.

Applicant notes that the compounds recited in Claims 50 (pergolide) and 55 (levodopa/carbidopa) of the subject application are not selective serotonin and nor-adrenaline re-uptake inhibitors. Furthermore, Claims 50 and 55 are directed to pharmaceutical combined preparations for treating Parkinson Disease, while Claim 1 of Application No. 10/984,683 is directed to a method of treating a mood disorder.

Reconsideration and withdrawal of this rejection are respectfully requested.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/725,965. The claims have been subject to a restriction requirement. An Office Action on the merits of the application was issued on January 23, 2008.

2. U.S. Patent Application No. 10/752,423. The claims have been subject to a restriction requirement. An Office Action on the merits of the application issued on October 2, 2007.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007 and February 22, 2008.

4. U.S. Patent Application No. 10/580,962. An examination report has not yet issued in connection with this application.

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement (SIDS) is being submitted pursuant to 37 C.F.R. §1.97(c)(2) to supplement the IDSs filed on August 21, 2007, April 11, 2007 and August 10, 2005 in connection with the subject application.

CONCLUSIONS

In view of the preceding amendments and remarks, applicant respectfully requests that the Examiner reconsider and withdraw the rejections set forth in the October 19, 2007 Office Action, and earnestly solicits allowance of the claims under examination. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $705.00 is enclosed for the $525.00 fee for a three month extension of time for a small entity and the $180.00 fee for submitting an IDS. No other fee is deemed necessary in connection with the filing of this reply. However, if any other fee is required to maintain the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Please credit any overpayment to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: April 4, 2008
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By _____
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